H020
CHRONIC EXPRESSION OF OSTEOPONTIN IN CARDIOMYOCYTES LED TO DILATED CARDIOMYOPATHY

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Osteopontin (OPN) is not expressed in healthy heart while, its expression is dramatically increased in cardiomyocytes and inflammatory cells during cardiomyopathies and heart failure. However its role in the development of heart diseases is not known.

To understand whether OPN is involved in cardiomyopathy, we created a transgenic mouse (MHC-OPN) expressing recombinant OPN (rOPN) specifically in cardiomyocytes using aMHC promoter-directed OPN expression and tTA technology. In these mice, rOPN expression could be regulated by doxycyclin oral administration.

After birth, MHC-OPN young mice were phenotypically indistinguishable from their littermate controls, but most of them died early between the 8th and 15th weeks after birth with a half life of 12 weeks. However, less than 10% MHC-OPN mice survived and were still alive 30 weeks after birth. Inhibition of recombinant OPN expression by doxycyclin at the beginning of T cell infiltration (5 weeks after birth) or when DCM was initiated (11 weeks after birth) reduced myocarditis and thus avoided the early death.

Electrocardiography demonstrated atrio-ventricular and intra ventricular defects. Moreover, echocardiography showed left ventricular dilation without hypertrophy and a systolic dysfunction, as indicated by reduced left ventricular fractional shortening (control mice: 29,8±2,0%, n=13; and MHC-OPN mice: 13,7±4,0%, n=5; T test $p<0.05$). In vitro histology confirmed that mice died because of a dilated cardiomyopathy associated with a strong fibrosis.

By immunohistology, we demonstrated that OPN expression in cardiomyocytes induced an important cell infiltration including some macrophages and a large number of fibroblasts and activated CD4+ and CD8+ T cells.

All together these experiments suggested that chronic OPN expression is required for DCM development inducing Tcell activation and thus a chronic myocarditis resulting in the dilated cardiomyopathy.

Keywords: Dilated cardiomyopathy, myocarditis, osteopontin, transgenic mouse

H021
GENETIC DISRUPTION OF PROTEIN TYROSINE PHOSPHATASE 1B ATTENUATES BOTH MYOCARDIAL AND ENDOTHELIAL DYSFUNCTION IN MICE WITH HEART FAILURE

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We have shown previously that chronic, in vivo pharmacological inhibition of protein tyrosine phosphatase 1B (PTP1B) prevented both endothelial and cardiac dysfunction in mice with chronic heart failure (CHF). The present study was designed to test whether similar cardiovascular protective effects are present in mice genetically deficient for PTP1B.

CHF was induced by coronary ligation, either in wild type (WT) or PTP1B deficient (PTP1B-/-) BALB/c mice. After 2 months of ligation, echocardiographic analysis of left ventricular (LV) function and remodelling was performed, after which flow-mediated, NO-dependent vasodilatation (FMD) of mesenteric resistance arteries was evaluated.

In PTP1B-/- mice with CHF (n=13), compared to CHF WT mice (n=15) LV end diastolic diameter (LVEDD) and LV end systolic diameter (LVESD) were reduced (LVEDD: CHF WT 6.1±0.2; CHF PTP1B-/- 5.2±0.2 mm, $p<0.01$; LVESD: CHF WT 5.5±0.2; CHF PTP1B-/- 3.9±0.3 mm, $p<0.01$), while fractional shortening (FS) and cardiac output (CO) were increased (FS: CHF WT 10.9±1.6; CHF PTP1B-/- 22.7±2.5%, $p<0.01$; CO: WT 16.3±1.0; PTP1B-/- 22.2±1.1 ml/min, $p<0.05$). Genetic disruption of PTP1B was also associated with decreased collagen density. These hemodynamic and structural effects were observed in the context of identical infarct sizes.

Vascular studies showed that compared to CHF WT mice (n=15), CHF PTP1B-/- mice (n=16) displayed an increased FMD (CHF WT 5±1, CHF PTP1B-/- 19±4%, $p<0.05$). Additionally, in vitro downregulation of PTP1B (by a 3 day incubation with shRNA) also increased FMD in arteries isolated from CHF mice (max FMD; untreated: 6±2; scrambled shRNA: 7±2; PTP1B shRNA 27±2%, $p<0.01$).

Thus, genetic disruption of PTP1B prevent endothelial and cardiac dysfunction in CHF mice, suggesting that this enzyme may be a new interesting target for the treatment of CHF.

H022
FKBP12.6 OVEREXPRESSION IN MOUSE CARDIAC MYOCYTES OFFERS MINOR PROTECTION AGAINST PRESSURE OVERLOAD-INDUCED CARDIAC REMODELLING AND FAILURE

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Alterations in RyR2 function is a hallmark of heart failure (HF). Decreased FKBP12.6 binding to RyR2 has been put forward to explain the diastolic SR Ca2+ leakage observed in this condition. Previous work in the mouse has shown that cardiac FKBP12.6 overexpression protects against the development of myocardial infarction-induced heart failure. Using a mouse model of conditional cardiac-specific FKBP12.6 overexpression, we tested the hypothesis that this overexpression protects against transverse aortic constriction (TAC)-induced cardiac remodelling and failure.

Ten weeks after TAC, male transgenic (DT) and their littermates controls (Ctr) underwent heart catheterization. Ventricular expression of the hypertrophic gene program and calcium handling proteins were assessed by real-time PCR and Western blot, respectively.Ten weeks after TAC, the mortality rate was 23% in Ctr and 13% in DT (14/60 vs 5/39, ns). The percentage of mice with